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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,625	11/02/2006	Stephen J. Klaus	FP0617 US	7369

41385 7590 10/11/2011

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409 Illinois Street
San Francisco, CA 94158

EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
10/11/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,625	KLAUS ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,12-16 and 49* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 12-16 and 49* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Amendment

The amendment filed 8/1/11 has been entered into the record. Claims 2-11 and 17-48 have been cancelled. Claims 1 and 49 have been amended. Claims 1, 12-16 and 49 are pending and are under examination.

Claim Rejections Withdrawn

The rejection of claim 1, 12-13, 15-16, and 48-49 under 35 U.S.C. 102(e) as being anticipated by Klaus et al. US 2003/0153503 published Aug 14, 2003, filed Dec. 6, 2002 as evidenced by Skarpidi et al (Experimental Hematology 31 (March 2003) 197-203, cited previously) is withdrawn in view of the cancellation of claim 48 and the amendment to claim 1.

The rejection of claims 1, 12-16, and 48-49 under 35 U.S.C. 103(a) as being unpatentable over Klaus et al. US 2003/0153503 published Aug 14, 2003, filed Dec. 6, 2002 in view of Perrine et al. WO 93/18761, 1993, cited in IDS as evidenced by Skarpidi et al (Experimental Hematology 31 (March 2003) 197-203, cited previously) is withdrawn in view of the cancellation of claim 48 and the amendment to claim 1.

Claim Rejections Based on Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 12-13, 15-16 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Klaus et al. US 2003/0153503 published Aug 14, 2003, filed Dec. 6, 2002.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims are drawn to a method for treating hemoglobinopathy in a subject, the method comprising administering to the subject in need thereof a compound that inhibits hypoxia-inducible factor (HIF) prolyl hydroxylase wherein the compound is a structural mimetic of 2-oxoglutarate which increases expression of the gene encoding γ-globin in a bone marrow derived cell a hematopoietic stem cell or a blast –forming unit erythroid cell thereby treating the hemoglobinopathy in the subject.

Klaus et al discloses a method for treating a subject having anemia related conditions or disorders such as hemoglobinopathy such as abnormal hemoglobin such as thalassemia major and minor (beta thalassemia), sickle cell disease (sickle cell syndrome, sickle cell anemia) (paragraph 17, paragraph 77, p. 11 paragraph 80) comprising administering to a subject in need thereof a compound which inhibits HIF prolyl hydroxylase (see p. 2 paragraph 17-18) wherein the compound is a structural mimetic of 2 oxo-glutarate (paragraph 110 p. 14). Said 2 oxoglutarate mimetic inhibits (HIF) prolyl hydroxylase competitively with respect to 2 oxoglutarate and non-competitively with respect to iron (see paragraph 110).

The structural mimetics of 2 oxo-glutarate (paragraph 110 p. 14) inherently have the property of increasing expression of the gene encoding γ-globin in a bone marrow derived cell or hematopoietic stem cells or blast forming erythroid cells and thus administering the structural mimetic of 2 oxoglutarate increases the proportion of fetal hemoglobin relative to non-fetal hemoglobin produced by bone marrow derived cells or hematopoietic stem cells or blast forming erythroid cells. Klaus et al teaches the same active method steps of administering a structural mimetic of 2-oxoglutrate to a subject in need thereof in order to treat a hemoglobinopathy. The wherein clause " wherein the compound increases expression of the gene encoding γ-globin in a bone marrow derived cell a hematopoietic stem cell or a blast –forming unit erythroid cell"

merely expresses the intended result of the positively recited step of administering the inhibitor of HIF prolyl hydroxylase to a subject and is not given any weight. See MPEP 2111.04.

Applicants' arguments:

Applicants argue that the only citation in Klaus et al provided by the Examiner to evidence this contention (paragraph 80) recites various conditions, diseases, and disorders that may be associated with anemia. Klaus et al do not recite "a method for treating a hemoglobinopathy in a subject. As Klaus et al do not recite a method for treating a hemoglobinopathy, Klaus et al do not set forth explicitly or inherently each and every element in the present claims.

Response:

Applicants' arguments are carefully considered but are not persuasive. Klaus et al specifically discloses treating a hemoglobinopathy. For example:

See paragraph 17 below:

> [0017] The present invention specifically relates to methods for treating, preventing, or pretreating anemia in a subject. In one embodiment, the method comprises increasing endogenous EPO, including, in various embodiments, stabilizing HIFα, inhibiting 2-oxoglutarate dioxygenase enzyme activity, inhibiting HIF prolyl hydroxylase enzyme activity, etc.

Klaus et al defines "anemia" which encompasses hemoglobinopathy (abnormality in hemoglobin) in paragraph 77:

[0077] The term "anemia" as used herein refers to any abnormality in hemoglobin or erythrocytes that leads to reduced oxygen levels in the blood. Anemia can be associated with abnormal production, processing, or performance of erythrocytes and/or hemoglobin. The term anemia refers to any reduction in the number of red blood cells and/or level of hemoglobin in blood relative to normal blood levels.

Paragraph 98 discloses methods of increasing endogeouns EPO (erythropoietin) livels to treat conditions associated with anemia which include abnormal hemoglobin and paragraph 80 defines "anemic conditions" to include sickle cell disease, thalassemia major and minor.

[0080] The terms "anemic conditions" and "anemic disorders" refer to any condition, disease, or disorder associated with anemia. Such disorders include, but are not limited to, those disorders listed above. Anemic disorders further include, but are not limited to, aplastic anemia, autoimmune hemolytic anemia, bone marrow transplantation, Churg-Strauss syndrome, Diamond Blackfan anemia, Fanconi's anemia, Felty syndrome, graft versus host disease, hematopoietic stem cell transplantation; hemolytic uremic syndrome, myelodysplasic syndrome, nocturnal paroxysmal hemoglobinuria, osteomyelofibrosis, pancytopenia, pure red-cell aplasia, purpura Schoenlein-Henoch, sideroblastic anemia, refractory anemia with excess of blasts, rheumatoid arthritis, Shwachman syndrome, sickle cell disease, thalassemia major, thalassemia minor, thrombocytopenic purpura, etc.

Klaus et al discloses that the compounds that can be used in the methods of the invention include structural mimetics of 2-oxoglutarate. See paragraph 110:

[0110] Compounds that can be used in the methods of the invention include, e.g., structural mimetics of 2-oxoglutarate. Such compounds may inhibit the target 2-oxoglutarate dioxygenase family member competitively with respect to 2-oxoglutarate and noncompetitively with respect to iron. (Majamaa et al. (1984) Eur J Biochem 138:239-45; and Majamaa et al., supra.)

Therefore, even though Klaus et al does not recite the instant method as exactly written *ipsis verbis* in the same words in one paragraph or sentence, it is clear that there is a relevant and direct connection between the various paragraphs of Klaus et al as set forth above and in the prior rejection. Klaus et al anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 12-16, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaus et al. US 2003/0153503 published Aug 14, 2003, filed Dec. 6, 2002 in view of Perrine et al. WO 93/18761, 1993, cited in IDS.

Klaus et al discloses a method for treating a subject having anemia related conditions or disorders such as hemoglobinopathy such as abnormal hemoglobin such as thalassemia major and minor (beta thalassemia), sickle cell disease (sickle cell syndrome, sickle cell anemia) (paragraphs 17, 77 and p. 11 paragraph 80) comprising administering to a subject in need thereof a compound which inhibits HIF prolyl hydroxylase (see p. 2 paragraph 17-18) wherein the compound is a structural mimetic of 2 oxo-glutarate (paragraph 110 p. 14). Said 2 oxoglutarate mimetic inhibits (HIF) prolyl hydroxylase competitively with respect to 2 oxoglutarate and non-competitively with respect to iron (see paragraph 110). Please also see whole document.

The structural mimetics of 2 oxo-glutarate (paragraph 110 p. 14) inherently have the property of increasing expression of the gene encoding γ-globin in a bone marrow derived cell or hematopoietic stem cells or blast forming erythroid cells and thus administering the structural mimetic of 2 oxoglutarate increases the proportion of fetal hemoglobin relative to non-fetal hemoglobin produced by bone marrow derived cells or hematopoietic stem cells or blast forming erythroid cells. Klaus et al teaches the same active method steps of administering a structural mimetic of 2-oxoglutrate to a subject in need thereof in order to treat a hemoglobinopathy. The wherein clause " wherein the compound increases expression of the gene encoding γ-globin in a bone marrow derived cell a hematopoietic stem cell or a blast –forming unit erythroid cell" merely expresses the intended result of the positively recited step of administering the inhibitor of HIF prolyl hydroxylase to a subject and is not given any weight. See MPEP 2111.04.

Klaus et al does not teach that the hemoglobinopathy is β^{o} - or β^{+}- β thalassemia.

Perrine et al teach other types of β thalassemia such as βo - or β^{+}-. See p. 2 lines 16-30.

It would have been prima facie obvious to one of ordinary skill in the art to have used the method of Klaus et al to treat other β thalassemia disorders such as β^{o} - or β^{+}-, thus resulting in the instant invention with a reasonable expectation of success. The motivation to do so is that

Klaus et al teach that hemoglobinopathy such as abnormal hemoglobin such as beta thalassemia can be treated by administering HIF prolyl hydroxylase inhibitors such as hydroxamate or structural mimetics of 2 oxo-glutarate.

Applicants' arguments:

Applicant argues that the Examiner characterizes Klaus et al as disclosing "the same HIF prolyl hydroxylase inhibitors as claimed for treating the same condition in the claim i.e. hemoglobinopathy." (Office Action, page 9.) Applicants argue that Klaus et al does not recite methods for treating hemoglobinopathy in a subject and for the present claims to be obvious in view of Klaus et al, Perrine et al would have to provide some teaching or suggestion to use the methods of Klaus et al to treat hemoglobinopathy in a subject. Applicant argues that Perrine et al does not provide this link. Applicants argue that the present claims are not obvious based on the teachings of Klaus et al when considered alone or in view of Perrine et al.

Response:

Applicants' arguments are carefully considered but are not persuasive. Klaus et al specifically discloses treating a hemoglobinopathy. For example,

See paragraph 17 below:

> [0017] The present invention specifically relates to methods for treating, preventing, or pretreating anemia in a subject. In one embodiment, the method comprises increasing endogenous EPO, including, in various embodiments, stabilizing HIFα, inhibiting 2-oxoglutarate dioxygenase enzyme activity, inhibiting HIF prolyl hydroxylase enzyme activity, etc.

Klaus et al defines "anemia" which encompasses hemoglobinopathy (abnormality in hemoglobin) in paragraph 77:

[0077] The term "anemia" as used herein refers to any abnormality in hemoglobin or erythrocytes that leads to reduced oxygen levels in the blood. Anemia can be associated with abnormal production, processing, or performance of erythrocytes and/or hemoglobin. The term anemia refers to any reduction in the number of red blood cells and/or level of hemoglobin in blood relative to normal blood levels.

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Klaus et al discloses that the compounds that can be used in the methods of the invention include structural mimetics of 2-oxoglutarate. See paragraph 110:

[0110] Compounds that can be used in the methods of the invention include, e.g., structural mimetics of 2-oxoglutarate. Such compounds may inhibit the target 2-oxoglutarate dioxygenase family member competitively with respect to 2-oxoglutarate and noncompetitively with respect to iron. (Majamaa et al. (1984) Eur J Biochem 138:239-45; and Majamaa et al., supra.)

Therefore, even though Klaus et al does not recite "hemoglobinopathy" as exactly written, Klaus et al defines "anemia' to include any abnormality in hemoglobinopathy that leads to reduced oxygen levels. This is a hemoglobinopathy. Therefore, the combination of Klaus et al and Perrine et al renders the instant claims prima facie obvious.

Status of Claims

Claims 1, 12-16, and 49 are rejected. No claims allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is (571)272-9939. The examiner can normally be reached on M-F 8:30 am- 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Oluwatosin Ogunbiyi/
Primary Examiner, Art Unit 1645